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8. (Amended) A method of reducing an atherosclerotic plaque load in the vessels of a mammal comprising administering to a mammal in need of such reduction a progestational agent that has an effect on the function of the sex organs of said mammal less than that of medroxyprogesterone acetate, wherein said agent is administered in an amount sufficient to effect said reduction.

REMARKS

Reconsideration of this application and entry of the foregoing amendment are respectfully requested.

Claim 8 has been revised to define the invention with additional clarity. The claim as presented is fully supported by an enabling disclosure. That the claim has been amended should not be construed as an indication that Applicant agrees with any position taken by the Examiner. Rather, the revision is made merely to advance prosecution and Applicant reserves the right to pursue any deleted subject matter in a continuation application.

Claims 8 and 9 stand rejected under 35 USC 112, second paragraph, as allegedly being indefinite. Withdrawal of the rejection is believed to be in order in view of the above-noted claim revision and for the reasons that follow.

The Examiner objects to the phrase "effect on the sex organs … less than that of medroxyprogesterone". The phrase, as it appears in claim 8 as now presented, reads "effect on the function of the sex organs …".

As pointed out previously, one skilled in the art would fully appreciate the nature of the effects intended. Again, attention is directed to the portions of the Physician's Desk Reference (PDR) (1999) of record relating to medroxyprogesterone acetate (MPA). The PDR portions make clear the effects of MPA on the function of sex organs both from the standpoint of clinical pharmacology and adverse reactions. Applicant previously provided technical articles that describe the effects of MPA on the function of sex organs of various species of males (including primates). Submitted herewith are additional articles that describe the effects of MPA on the function of sex organs of females (see Croxatto et al, Contraception 54:79 (1996) and Whitehead et al, Obs. Gyn. 75(4)S:59S (1990)).

Given the PDR portions and representative technical publications provided, it will be evident that the effects of MPA on the ovary and uterus are well established. In the ovary, it prevents follicular maturation and ovulation by inhibiting production of gonadotropins. In the uterus, it induces uterine endothelium to become secretory and

vascular, leading to menstrual bleeding irregularities. The effects of medroxyprogesterone on testicular function are also well established. It results in a reduction in the level testosterone and induces impotence. No indefiniteness results in the use of the present language.

The effects of progestational agents on uterine function can be measured by the affinity of the binding of the progesterones to the rabbit uterus. Terenius (copy attached) teaches that 17-hydroxyprogesterone (recited in claim 9) and related progestational agents have a lower affinity for the rabbit unterus than does MPA.

Given the foregoing, basis for the Examiner's concern is not seen and reconsideration is requested.

Claims 8 and 9 stand rejected under 35 USC 103 as allegedly being obvious over Aristoff et al in view of Kuzuya et al. Withdrawal of the rejection is submitted to be in order for the reasons that follow.

The claims relate to a method of reducing atherosclerotic plaque load in the vessels of a patient.

As the Examiner appreciates, Aristoff relates to a method of inhibiting angiogenesis. The method of the reference involves the administration of a combination of a suramin-type compound and an angiostatic compound, 17 α-hydroxyprogesterone being an example of an angiostatic

compound (administration of an angiostatic compound alone is not taught). As the Examiner appreciates, the reference does not teach the use of 17-hydroxyprogesterone to reduce atherosclerotic plaque. Indeed, the article says nothing of reducing plaque load but rather refers to the treatment of diseases of neovascularization using the suramin/angiostic compound combination. Accordingly, nothing in the citation would have suggested the use of the present progestational agents in the claimed method.

The Examiner relies on Kuzuya et al to cure the deficiencies of Aristoff et al. Respectfully, Kuzuya et al provides no such cure.

First Kuzuya et al reports the results of *in vitro* - not *in vivo* - studies, such studies in the context of the present invention are of questionable therapeutic relevance. Further Kuzuya et al makes reference to the "association" between neovascularization and atherosclerotic plaque formation. It does not demonstrate that neovascularization is causative. Additionally Kuzuya et al repeatedly couches the "role" of neovascularization in atherosclerotic plaque formation in terms of it being "possible" (see title) or "postulated" (see abstract). Indeed, in the abstract, it is stated that "the mechanism and stimulus for neovascularization in atherosclerotic

plaque are unknown". On page 665, right column, first paragraph, it is acknowledged that "little is known about pathogenesis of microvessels in atherosclerotic plaque". Thus, by Kuzuya et al's own statements, it is clear that these authors themselves do not view their studies as demonstrating that "angiogenesis is known to be a contributive factor in the progression of atherosclerotic plaque", as the Examiner contends.

It is important to note that the very real possibility exists that the neovascularization "associated" with plaque formation is actually a protective mechanism. That is, new blood vessel formation in the area of a plaque may result from the need for increased blood flow in that area. Nothing is found in Kuzuya et al that is inconsistent with this possibility.

In view of the above, reconsideration is requested.

Claims 10-13 stand rejected under 35 USC 103 as allegedly being obvious over Cincotta in view of Gruijter et al. Withdrawal of the rejection is submitted to be in order for the reasons that follow.

As pointed out previously, Cincotta relates primarily to a method of reducing restenosis in a mammal undergoing a non-bypass invasive procedure. As indicated in the paragraph bridging columns 1 and 2 of the citation,

restinosis results from a complex series of events. The method of inhibiting restenosis comprises administering a dopamine-potentiating/prolactin-reducing compound (halperidol being an example of a prolactin enhancer) to reduce blood prolactin levels during at least a portion of the daylight hours and continuing that administration during the healing period of the injury.

The Examiner states: "Cincotta et al. does not expressly teach the use of haloperidol specifically in a method of reducing atherosclerotic plaque."

The Examiner relies on de Gruijter et al to cure the failings of Cincotta. de Gruijter et al, however, is an *in vitro* not an *in vivo* study and thus, as indicated above, of questional relevance to the claimed therapeutic method.

Further, de Gruiter et al is based on monocyte binding studies. Monocytes are naturally adherent cells, making such binding studies difficult to interpret.

Of further significance is the fact that the beneficial effects of haloperidol on plaque load described in the present application cannot be ascribed to a reduction in serum triglyceride levels (see Example 1).

In view of the above, reconsideration is requested.

Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached

page is captioned "**Version With Markings To Show Changes Made**."

This application is submitted to be in condition for allowance and a Notice to that effect is requested.

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE CLAIMS:

8. (Amended) A method of reducing an atherosclerotic plaque load in the vessels of a mammal comprising administering to a mammal in need of such reduction a progestational agent that has an effect on the function of the sex organs of said mammal less than that of medroxyprogesterone acetate, wherein said agent is administered in an amount sufficient to effect said reduction.